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E D I T O R I A L

AN EQUAL THREAT TO CIVILIZATION

ALTHOUGH the civilized world is currently preoccupied with the hazards and the possibility of nuclear warfare, there is another threat to humanity of an equal magnitude which continues almost unnoticed. The fact is that the mere mention of this hazard causes most people to shrug it off as one not deserving attention. We speak of the population explosion which, while it presently is not any serious threat in the United States, is an even greater threat to certain countries such as India than is the hydrogen bomb itself!

In the United States, most businessmen rub their hands in glee at the thought of increased population and the increased demand for goods and services which this increase is certain to bring. While in the U. S., we have not as yet reached the limit of our industrial capacity and can for a time at least manage to compensate for the population increase, this is not the case all over the world. That this problem is beginning to alarm many of our friends overseas is evident by some of the recent actions taken both by individual governments and in the United Nations.

A recent editorial in *The Eastern Pharmacist* gave certain facts and figures which drive home the problem with great force and clarity. In the decade, 1941-51, life expectancy in India was about 32. (Here, we wish to digress long enough to point out that this was ours in the United States as early as 1900.) In the five year period, 1951-56, life expectancy in India was 38 and, now in 1961, it is 42.5. This compares with a life expectancy in the U. S. of about 75 at the present time. The editorial in *The Eastern Pharmacist* continued by pointing out that the growth and improvement of medical care facilities have been impressive but they still are pitifully small to serve a nation of 500 million people. India has only 60 medical colleges and 13 colleges of pharmacy with a population almost three times ours, and their production of drugs is but a mere trickle compared to the vast production here in the United States. Even so, India since becoming independent, has greatly improved its medical care program, and done so under tremendous difficulties imposed by the very staggering proportions of the problem and the gross poverty of its people.

Here, we wish to quote part of the editorial of *The Eastern Pharmacist:*

> "But this picture has another side which is dismal. Through better care of the public health the population has begun to grow faster creating many social and economic problems. It is notorious that in backward countries, including India, birth rate has always been higher than the death rate. Now if through better medical services the death rate is arrested and expectancy of life raised, it is evident that population will grow more quickly than before. Some thing has to be urgently done to control the birth rate and this the Government has, despite best efforts, failed to do so far. Family Planning remains to be the most important problem with which India is confronted. . . . As the authorities admit 'unless stability is reached between death rate and birth rate all our plans may be defeated.' "

While the magnitude of this problem is inescapable, its solution may be even more difficult than the prevention of nuclear war. Yet, by a strange anomaly, unless the population problem is solved, it may in time lead to nuclear war. The prevention of the total destruction of the human race by nuclear bombs requires only good will and brotherhood practiced among all peoples of the world, but controlling the world's population involves the mass exercise of individual restraint or the application of coercive methods on whole populations. Individual restraint can come only after a long program of education which is itself difficult to accomplish with the underprivileged and uneducated masses. The application of coercive controls would inflict on humanity a degree of slavery which would be intolerable and likely lead to revolution. While some foresee the eventual use of an antifertility pill, it is not too certain that these will be taken voluntarily without extensive education and indoctrination and, even then, those with education and a social consciousness would be most likely to curtail their offspring than would the uneducated and the illiterate. Thus would population continue to die off at the top with social retrogression the end result. We do not know the answer to this problem any more than we know any absolutely certain way to prevent nuclear war. We reiterate that the problems are of equal magnitude and, as such, they deserve equal attention by all those who are concerned with the future of human civilization.

L. F. Tice

DICHLOROISOPROTERENOL AND THE BETA ADRENERGIC RECEPTOR *

By Eugene E. Vogin ** and Walter W. Baker ***

THE theory of the chemical transmission of the nervous impulse requires that there exist on the effector cell an area or substance specifically designed to react with the chemical transmitter (1). The transmitter migrates to this area and combines with an acceptive material and, thus, the specific response of the effector cell is called forth.

Langley (2) was the first to postulate that "nerve impulses" and drugs act by combining with a receptive substance. Langley concluded that a chemical combination occurs between a drug and a constituent of the cell that he called a "receptive substance." In a like manner, the adrenergic transmitter combines chemically with the receptive substance to evoke an effector response.

The intimate nature of the receptive substance has not yet been determined. Langley conceived of it along the lines of Ehrlich's side-chain theory. Thus, a side chain, or portion of a molecule of the cellular substance, exists for which the transmitter or drug has a special affinity. The best available evidence indicates that the receptor is involved in an enzymatic process (1). It may be an enzyme itself, or a side chain of the protein enzyme. It most probably is involved in an enzymatic energy transport process. Experimentation has further shown that the receptor is an integral part of the effector cell.

The simplest method for describing adrenergic receptors would be to make a sharp distinction between excitatory and inhibitory ones. A critical study of the adrenergic receptors was made by Ahlquist (3) in 1948. On the basis of his observations of the actions of epinephrine (E), norepinephrine (NE), and isoproterenol (I) on various effectors, he concluded that there existed two types of receptors: (a) an *alpha* receptor, which is mainly excitatory and usually blocked by the classical adrenergic blocking agents such as the ergot alkaloids, dibenamine, and benzodioxanes, and (b) a *beta* receptor, which is

* This review was fostered by a series of lectures on Neurohumoral Mediators at the Philadelphia College of Pharmacy and Science.

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mainly inhibitory, and until the advent of dichloroisoproterenol (DCI) could not be blocked by the use of adrenergic blocking agents.

Ariens and Simonis (4) showed that the size of the chain substituted on the nitrogen of the phenethylamines was a factor determining the specificity of these compounds with respect to the type of adrenergic receptor that will be stimulated. These investigators postulated that, as the length of the substituted chain increases, the phenethylamine will have a greater affinity for the *beta* receptor than for the *alpha* receptor. Since Ahlquist's (3) original classification of adrenergic receptors, it has been known that the order of reactivity for the *alpha* receptor is (NE)>(E)>(I) and, for the *beta* receptor, (I)>(E)>(NE). From the structures illustrated in Fig. 1, it can be seen that (NE) is a primary amine, (E) is a methylated secondary amine, and (I) is an isopropyl substituted secondary amine. This correlation between activity and structure therefore tends to substantiate the hypothesis of Ariens and Simonis.

(NE) is predominantly an *alpha* receptor stimulant; (E) affects both *alpha* and *beta* receptors, as exemplified by its biphasic effect on blood pressure; and (I) is predominantly a *beta* receptor stimulant.

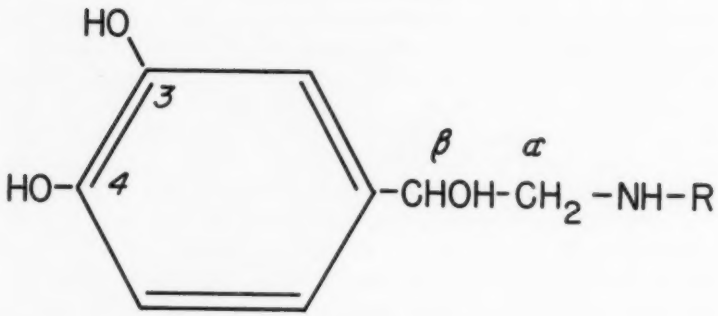
The following table lists the effects of adrenergic stimulation upon *alpha* and *beta* receptors as classified by Ahlquist (3):

Alpha Receptor	*Beta Receptor*
Vasoconstriction of Cutaneous Vessels	Vasodilation of Skeletal Vessels
Myocardial Ectopic Excitation	Cardioacceleration
Contraction of Radial Muscles of the Iris	Increased Cardiac Contractility
Contraction of Arrector Pili	Bronchiolar Dilatation
Glycogenolysis	Myometrial Relaxation
Intestinal Smooth Muscle Relaxation	Smooth Muscle Relaxation (Aorta, Stomach)
Other Smooth Muscle Contraction (Aorta, Stomach, Uterus)	

With the advent of DCI in 1958 (5), it is now possible to delineate and more fully explain the occurrence, nature, and action of the *beta* adrenergic receptors. The purpose of this report is to review the work that has been done in elucidating the role of the *beta* adrenergic receptors as related to the activity of the sympathomimetic amines.

FIGURE I

SYMPATHOMIMETIC AMINES

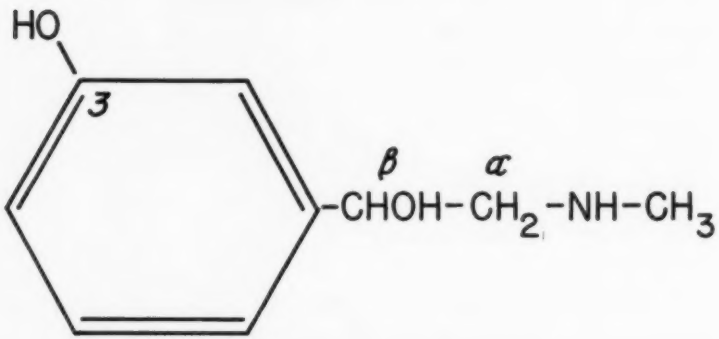


R = H; beta-hydroxy-3,4-dihydroxyphenethylamine
NOREPINEPHRINE (NE)

R = CH_3; beta-hydroxy-N-methyl-3,4-dihydroxyphenethylamine
EPINEPHRINE (E)

R = $CH(CH_3)_2$; beta-hydroxy-N-isopropyl-3,4-dihydroxyphenethylamine
ISOPROTERENOL (I)

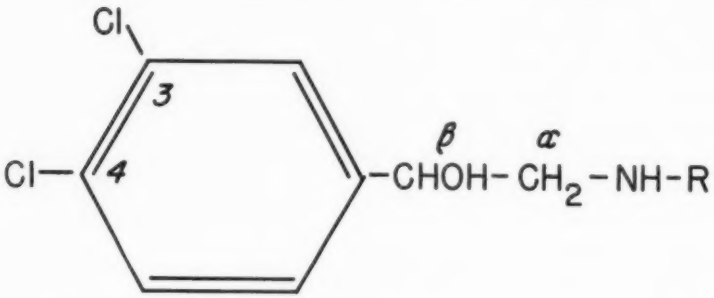
R = CH_2-CH_3; beta-hydroxy-N-ethyl-3,4-dihydroxyphenethylamine
ETHYLNOREPINEPHRINE (ENE)



beta-hydroxy-N-methyl-3-hydroxyphenethylamine
PHENYLEPHRINE (PE)

FIGURE 11

DICHLORO ANALOGS OF THE SYMPATHOMIMETIC AMINES



R = H; beta-hydroxy-3,4-dichlorophenethylamine
DICHLORONOREPINEPHRINE (DCNE)

R = CH_3; beta-hydroxy-N-methyl-3,4-dichlorophenethylamine
DICHLOROEPINEPHRINE (DCE)

R = $CH(CH_3)_2$; beta-hydroxy-N-isopropyl-3,4-dichlorophenethylamine
DICHLOROISOPROTERENOL (DCI)

Pharmacology of DCI

Powell and Slater (5) have shown that DCI will cause a transient decrease or no change in blood pressure in dogs. After DCI, the pressor effects of challenge doses of (E) and (NE) were not affected, but the depressor effect of (I) was blocked. DCI has no effect on the pressor responses to carotid occlusion or contraction of the nictitating membrane induced either by (E) or preganglionic stimulation.

DCI exerted no effect on normal uterine movements. However, uterine relaxation produced by (E) or (I) was inhibited or substantially reduced. Both DCI and (I) caused a transient increase in blood flow but, after administration of DCI, (I) only caused an increase flow rate of 40 per cent of that which had been observed prior to DCI treatment.

DCI blocked the inhibitory effect of (E) on isolated rabbit intestine but not the relaxation produced in the rat uterus, except in high doses in which the analog itself caused considerable decrease in tone. The dichloro analog caused only a slight decrease of intra-

pulmonary resistance to air-flow in the ergotoxine treated decerebrate-pithed animal, but had no effect on pilocarpine bronchoconstriction. The administration of DCI blocked the usual (E) or (I) release of this bronchoconstriction. DCI also inhibited both (E) and (I) relaxation of the pilocarpine-induced spasm of the guinea pig tracheal chain. This action appeared to be competitive since large doses of (E) could partially overcome the blocking action of DCI.

From these experiments, Powell and Slater concluded that DCI, in all probability, combines with certain "adrenergic inhibitory receptor sites" without itself causing pronounced physiological effects.

Cardiovascular Effects

The classification of the adrenergic receptors of mammalian hearts raises a special problem in the pharmacological description of the sympathetic nervous system, a problem implied in the following statement from Goodman and Gilman (6)—"Dibenamine and Dibenzyline effectively prevent the excitatory responses of smooth muscle and exocrine gland cells to adrenergic stimuli; they fail to block inhibitory response of smooth muscle and also do not prevent the chronotropic and inotropic responses of mammalian cardiac muscle . . ."

Because of this seemingly paradoxical situation, various schemes of classification have been proposed to resolve these differences. According to Ahlquist (3), the excitatory responses of cardioacceleration and augmentation of cardiac contractility are attributable to the *beta* receptors, while the myocardial ectopic excitation is related to the *alpha* receptor.

Since the classification of drug receptors depends on the use of selective blocking drugs to differentiate one receptor from another, the status of adrenergic cardiac receptors had been in doubt. Although some investigators (7-9) have observed inhibition of the myocardial stimulant effect of sympathomimetic amines in mammalian hearts by some adrenergic blocking agents, other workers have not (10). Furthermore, the blockade when observed was not consistent, required large doses of the blocking compounds, and was not represented in the actions of all members of this class of drugs.

Stimulated by the observations of Powell and Slater (5), Moran and Perkins (11, 12) investigated the effect of DCI on the selective blockade of the positive inotropic and chronotropic effects of adren-

ergic stimuli. These investigators have shown that DCI selectively blocks the cardiac positive inotropic and chronotropic effects of adrenergic stimuli in dogs with intact circulatory systems and in isolated rabbit hearts. In dogs, complete blockade of the positive inotropic effects of (E), (NE) and (I), and of supramaximal stimulation of the cardiac sympathetic nerves is obtained with cumulative doses of DCI of 3 mg./Kg. and greater. Depression of contractile force was frequently observed in response to sympathomimetic amines and to sympathetic nerve stimulation after administration of large doses of DCI. The positive inotropic effects of digoxin, calcium chloride, or theophylline were not altered in any manner by pretreatment with DCI. This agent also blocked the positive chronotropic effects of (I). In isolated rabbit hearts, DCI has qualitatively the same blocking action on the effects of the catecholamines, but not on those of calcium, theophylline, or ouabain. The dichloro analogs of (E) and (NE) have similar blocking actions as those of DCI, but are less potent.

Although DCI initially stimulates the heart, the administration of subsequent doses depressed the myocardium. DCNE exerted a similar effect in the dog, but in rabbits, like DCE, it produced only depression. The cardiac depressant effect of these agents was not antagonized by atropine.

The vasopressor effect of (E) in dogs was potentiated by DCI; that of (NE) was not affected; and that produced by sympathetic nerve stimulation was blocked. The vasodepressor effect of (I) was completely blocked, but not reversed by DCI.

On the basis of the selective blockade by DCI of the excitatory effects of adrenergic stimuli on the heart and their inhibitory effects on other organs [e.g., the vasodepressor effect of (I)] and the lack of blockade of adrenergic vasopressor action, Moran and Perkins concluded that the adrenergic receptors of mammalian hearts are functionally homologous to the adrenergic inhibitory receptors of other tissues. This conclusion agrees with the hypothesis of Ahlquist that the cardiac inotropic and chronotropic sympathetic receptors are of the *beta* type, receptors which subserve inhibitory functions in other organs, in contrast to the *alpha* receptors which subserve sympathetic excitatory responses in all organs except the heart.

Using cat papillary muscle preparations, Dresel (13) also found that small doses of DCI increased cardiac force and that larger doses

antagonized the positive inotropic effect of (E). Furchgott *et al.* (14), using the same preparation and the isolated guinea pig atrium, confirmed the antagonism exhibited by DCI of the positive inotropic effects of both (E) and (NE). Furthermore, they showed that this antagonism was of a longer duration than the inhibitory effects of DCI itself. The inhibition produced by DCI was shown to be reversible since very high doses of catecholamines immediately after DCI again exhibited a positive inotropic effect.

Fleming and Hawkins (15, 16) studied the interaction between DCI and (E) on heart rate. These investigators found a definite correlation between small doses of (E) and moderate doses of DCI. Although the two effects summated, there was a progressive reduction in absolute response of heart rate increase to (E) in the presence of DCI. This phenomenon was attributed to the interaction termed "competitive dualism" by Ariens, *et al.* (17); that is, competitive interaction between two active drugs acting on the same receptor. Fleming and Hawkins (15) have also shown that the cardiac response to DCI is dose dependent. Low doses (less than 2 μg.) have no effect; at moderate doses (5 μg. to 3 mg.), the drug has sympathomimetic amine properties; and, at high doses (7 to 40 mg.), exhibited inhibitory and/or blocking activity on the myocardium.

Hull *et al.* (18) reported that DCI, given after the *alpha* adrenergic blocker, Dibenzyline, produced a depresser response. Following DCI-Dibenzyline pretreatment, injections of (E) and (NE) were not blocked as with Dibenzyline alone, but the pressor responses elicited were in the range of 50 to 75 per cent of control levels. If further doses of Dibenzyline were given, the pressor response to challenge doses of catecholamines was again decreased, but the response remained blocked.

These findings indicated that DCI alters not only the inhibitory *beta* adrenergic responses, but also the excitatory effects of (E) and (NE) after adrenergic blockade. This is especially interesting since the Dibenzyline blockade is generally considered to be of the non-equilibrium type. Yet, administration of DCI immediately restored the vasopressor actions of (E) and (NE). The specific nature of the observed antagonism between adrenergic blockade and DCI is still unknown. However, the possibility exists that the adrenergic blocking agents are displaced from the excitatory receptors by DCI, permitting their accessibility to the pressor amines. The other possibility

is that DCI may block only inhibitory receptors, permitting a greater concentration of the injected catecholamines to overcome an incomplete block of the excitatory receptors.

Walz *et al.* (19, 20) demonstrated that infusions of sympathomimetic amines produced a reversal of the response to challenging doses of (I). One of the most potent agents producing this reversal was shown to be phenylephrine (PE). At increased dose, (PE) decreased the depressor and increased the pressor response to (I). This vasomotor reversal was performed in acute and chronic spinal dogs, adrenalectomized dogs, and spinal animals (transection at C-2 or C-6).

If the heart had a decisive role in the production of this phenomenon, then reversal of (I) by (PE) after DCI should not be seen. The results obtained after pretreatment with DCI suggest that the heart is not a major component in this reversal. On this basis, and the fact that (I) reduced peripheral vessel resistance before (PE) and increased it after (PE), it appears that the cause of (I) vasomotor reversal is primarily due to changes in the response of the peripheral smooth vasculature.

Nictitating Membrane

Dibenzyline has been regarded classically as an irreversible adrenergic blocking agent of excitatory (*alpha*) receptors in the vasculature and nictitating membrane. Eltherington and Horita (21) observed that, after blockade of the smooth muscles of the blood vessels by Dibenzyline, subsequent injections of DCI caused a return of the (E) pressor response from 50 to 100 per cent of control values. This drug interaction is true with respect to blood pressure effects in anesthetized dogs and cats. The smooth muscle of the cat nictitating membrane, however, does not react in the same manner. Once adrenergic blockade had been established, DCI did not produce a return of the membrane contraction following the administration of challenging doses of (E).

This observation along with the original observations of Powell and Slater (5) more fully substantiate the fact that the sympathetic receptor of the smooth musculature of the nictitating membrane is an *alpha* receptor.

Intestinal Receptors

In 1948, Ahlquist (3) assigned the *alpha* receptor to the smooth musculature of the intestine. The characteristic intestinal response to adrenergic stimulation is a prompt cessation of rhythmic segmental contractions, lasting for only a short duration. Large doses of an *alpha* adrenergic blocking agent have been shown to produce partial to complete blockade of the intestinal response to (E) only occasionally (22); whereas, the response to (PE) is consistently blocked, and the response to (I) is not affected.

DCI itself produced intestinal inhibition for approximately 30 minutes when injected as a single dose. However, if infused, the effect of DCI as an intestinal inhibitor is decreased. DCI does not block the effects of (E) or (PE), but consistently inhibited the response to (I). The combination of DCI and the adrenergic blocking agent dibozane blocked (E), (PE), and (I).

From the data, it appeared evident that the intestine has both *alpha* and *beta* receptors, either of which will produce intestinal inhibition when stimulated.

In additional experiments (23, 24), Levy and Ahlquist showed that DCE and DCNE has qualitatively the same effects as DCI on intestinal inhibition. DCI was also shown to block the intestinal inhibition of other *beta* receptor activators such as Nylidrin.

Glycogenolysis Receptors

As stated previously, the usual potency ratio for *alpha* receptor stimulation is (NE)>(E)>(I) and, for *beta* receptors, (I)>(E)>(NE). The potency ratios for hyperglycemic action *in vivo* are (E)>(NE)=(I) (25, 26). Thus, there is a considerable deviation from the usual pattern which tends to invalidate the dual receptor theory. However, one might expect an order of potency as noted if it is assumed that for the full glycogenolytic effect stimulation of both *alpha* and *beta* receptors is necessary. (E), activating both receptors, would be a stronger glycogenolytic agent than either (NE) or (I). van der Pol (26) has confirmed this hypothesis by demonstrating a synergistic effect between (NE) and (I) on each other's hyperglycemic effect and thus potentiate each other's hyperglycemic action. Using DCI, Claassen and Noach (27) have been able to ascertain the *beta*-mimetic contribution to the hyperglycemic action of (E).

It has been shown that DCI, while having a slight hyperglycemic action of its own, reduced the (E) and (I) hyperglycemia, while leaving the hyperglycemic action of (NE) unaffected.

It therefore appeared evident that DCI competitively inhibits the glycogenolysis initiated by *beta* receptor activation. This has been confirmed by McCutcheon (28).

Effect on Phosphorylase Activation

Hess and Haugaard (29) and Kukovetz *et al.* (30) reported a correlation between the increased contractile force of cardiac tissue and phosphorylase activation induced by sympathomimetic amines in isolated perfused rat hearts. Mayer and Moran (31) have since shown that DCI could prevent the positive inotropic and phosphorylase activating effects of (E) and sympathetic nerve stimulation. These investigators have also shown that only adrenergic stimuli capable of increasing cardiac contractile force will augment myocardial phosphorylase activity. DCI alone augments contractile force but not phosphorylase activity.

The fact that DCI blocked both physiological and biochemical responses to catecholamines and that reserpine, presumably by depleting catecholamines (32, 33), prevented both the inotropic and phosphorylase activating effects of sympathetic stimulation seemed to support the concept that the adrenergic receptor for enzyme activation is similar to that for augmentation of contractile force; namely, the *beta* receptor.

Interaction of DCI and Other Pharmacologic Agents

Drinnon and associates (34-36) elucidated the probable mode of action of isoxsuprine with the aid of DCI. It was shown, by antagonism studies, that the positive inotropic and chronotropic effects of isoxsuprine are principally due to *beta* receptor stimulation; whereas, the vasodilator action was independent of *beta* adrenergic receptor stimulation.

Kiplinger *et al.* (37) have shown that DCI would not affect the biphasic blood pressure response of the choline antagonist 2-amino-2-methyl propanol (2-AMP) in the cat. They, therefore, concluded that 2-AMP mediates its vascular effects through a direct action on peripheral receptors.

Kumar and Sheth (38) reported that, while DCI possesses positive inotropic and chronotropic effects, it will abolish those of (E). Also, when DCI was added to quinidine treated stationary atria *in vitro,* the excitatory action of acetylcholine was abolished. These findings indicated that the excitatory effect of acetylcholine on quinidine treated atria was due to (E) release.

Farah and Tuttle (39) have shown that glucagon has positive inotropic and chronotropic effects similar to (E); tachyphylaxis develops upon repeated administration in a manner analogous to the long-acting amines. By using DCI to reduce the effects of glucagon, it seemed that the probable myocardial mode of action of glucagon was stimulation of the *beta* adrenergic receptor.

DCI has also been reported to block ouabain-induced cardiac arrhythmias (40), provide protection against injections of bacterial endotoxin (41), reduce (I) stimulated formation of adenosine-3′5′-phosphate (42), and antagonize the pressor effects of mephenteramine (43).

Criteria for Beta Adrenergic Blocking Activity

Levy and Ahlquist (44) used DCI to elucidate and compare the cardiovascular responses of ethylnorepinephrine (ENE) and (I) as a means of establishing criteria for *beta* adrenergic blocking agents. (ENE) stimulated both the *alpha* and *beta* receptors but, unlike (E), its effect was more predominant upon the *beta* receptor in that the biphasic blood pressure response consisted of an initial transient pressor response followed by a more prolonged depressor response. After DCI, not only was the depressor component abolished, but (ENE) also produced a sustained increase in peripheral resistance. In (PE)-treated dogs, DCI markedly reduced the pressor and positive chronotropic effects of (I) and (ENE).

(ENE) caused *beta* receptor predominance, producing primarily vasodilation, tachycardia, and a depressor response. Blockade of the *beta* receptors by DCI unmasked the effect of (ENE) on the *alpha* receptors; thus, (ENE) became a pressor and vasoconstrictor agent. DCI, as previously shown, also blocked the depressor effect of (I).

From these effects, Levy and Ahlquist have proposed the following criteria for *beta* adrenergic receptor blockade: (a) The conversion of the depressor response of (ENE) to a pressor response

and (b) The diminution but not the reversal of the (I) depressor response.

In summary, the use of DCI has fostered a more complete characterization of the role of the *beta* adrenergic receptor and a better understanding of the action of various pharmacologic agents.

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HISTOLOGICAL STUDIES OF THE GENUS LAVANDULA

Part IV. Section SPICA

Comparative Histology of the Leaves of Lavandula officinalis Chaix, L. latifolia Vill., and L. lanata Boiss

By J. K. Bhatnagar * and Marin S. Dunn **

Introduction

SPECIES of the genus Lavandula are grouped into five sections. The first three sections; namely, *Stoechas, Spica,* and *Pterostoechas,* were originally constituted and described by Gingin de Lassaraz. The fourth section, *Chactostachys,* was added by Bentham, and the last, *Subnuda,* was first described by Chaytor (1).

Species of the section, *Spica,* are found in wild state in the northwestern region of the Mediterranean, especially in the south and southeast of Spain, in eastern Pyrenees and southern maritime provinces of France, in the north and northcentral parts of Italy, in Sicily, Corsica, and a few other places.

The species of this section are distinguished from species of other sections by their many-flowered verticils; uniform, fertile bracts; by the presence of bracteoles; by the length of the corolla tube which is almost twice the length of the calyx; and by the nongelatinous outer coating of the nutlets.

However, due to the ease and the frequency of hybridization between the species within the section, and between the species of this section and the species of other sections, it is not always easy to

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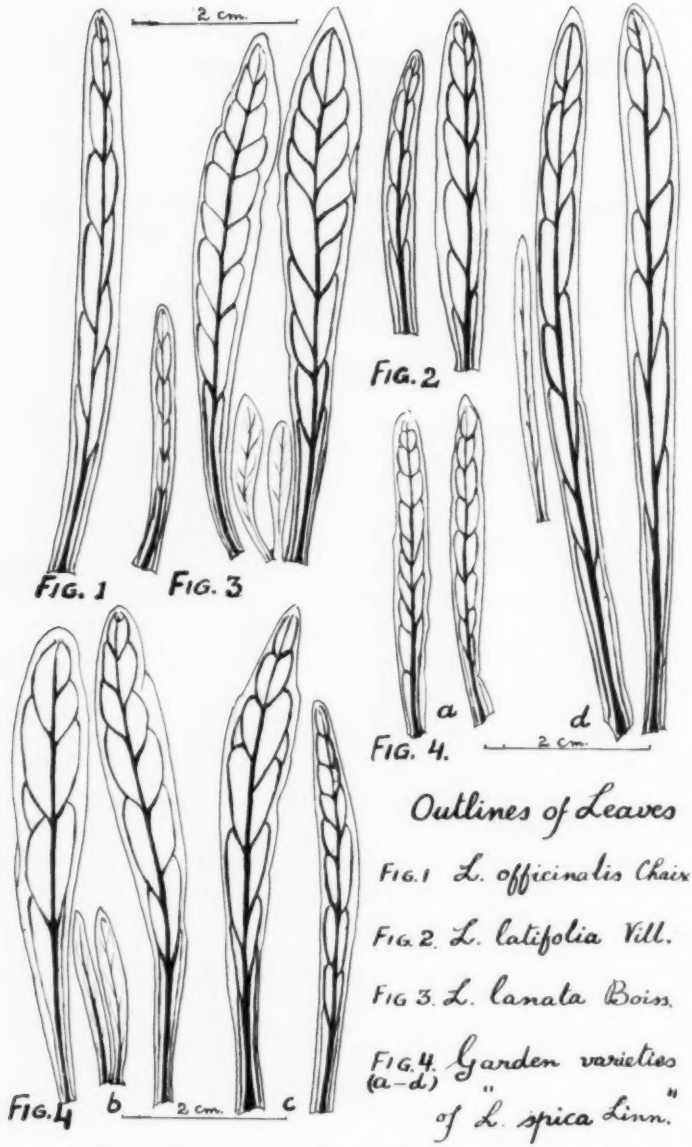
PLATE I.



Figs. 1-4. Outlines of the leaves without the indumenta: 1. *L. officinalis*, 2. *L. latifolia Vill.*, 3. *L. lanata Boiss.*, and 4. (a-d) Leaves of the garden varieties of *L. spica*.

identify these plants by their morphological characteristics alone. It is not surprising that the literature dealing with the nomenclature of these species is full of confusing, and sometimes conflicting, names and synonyms. The name, *Spica,* itself is an example of the prevailing confusion in the naming of these species.

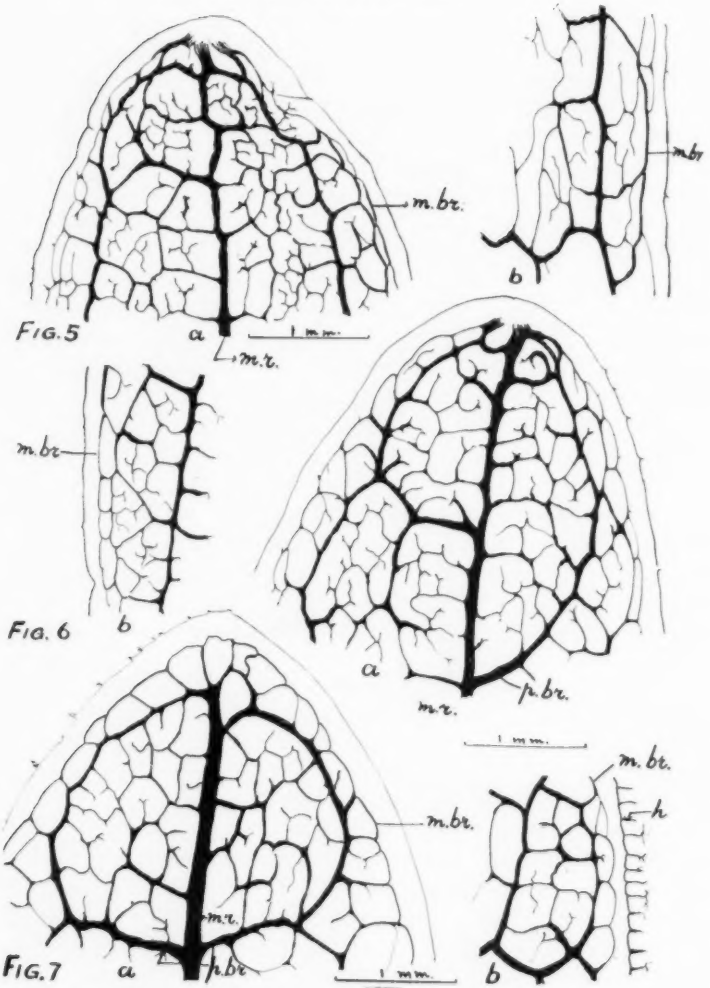
Linnaeus originally described two varieties of the species *L. spica,* namely, *L. spica* var. α *Linn.* (true Lavender), and *L. spica* var. β *Linn.* (Spike). However, the later taxonomists used the name *L. spica Linn.* indiscriminately for either of the two varieties with the result that this name became very ambiguous for taxonomic purposes. The International Botanical Congress in its session held in 1930 at Cambridge decided to drop the use of all ambiguous names. Accordingly, therefore, the correct name for *L. spica* var. *Linn.* is *L. officinalis Chaix* and, for *L. spica* var. β *Linn.,* the correct name is *L. latifolia Vill.* (2). Chaytor in her taxonomic studies of the genus Lavandula used the new names for the species included in the section, *Spica* (i.e., *L. officinalis Chaix, L. latifolia Vill.,* and *L. lanata Boiss.*), and the present authors have followed the same nomenclature in this report.

It is regrettable that the name *L. spica Linn.* is still being used in many gardens and herbaria. From the material labelled as *L. spica,* it has not always been possible to determine the exact species of the plant yielding the material. It is hoped that the plants or the specimens thus labelled will be given their correct name in not too distant a future.

The existing key (1) for the identification of the species of this section is primarily based on the branched or unbranched condition of the peduncles, and on the number of the veins and the indentations in the calyx tube. The morphological description of the leaves of these species is quite inadequate for identification purposes.

Reports dealing with the histology of these species are few in number. Mäckel (3) has been reported to have studied the hair characteristics of *L. officinalis* and *L. lanata,* together with those of *L. stoechas* and *L. pedunculata,* and to have used this characteristic to determine the source of Spanish Lavender which he found to be the leaves of *L. lanata.* Unfortunately, the present authors lacked access to a source from which the original text of Mäckel's article could be obtained. This report is based entirely on the studies conducted by the authors.

PLATE II.



Figs. 5-7. The terminal (a) and the marginal (b) venation of the leaves: 5. *L. officinalis*, 6. *L. latifolia*, and 7. *L. lanata* respectively.

(h, nonglandular hair; m.br., marginal branches; m.r., midrib; p.br., primary branches.)

Material and Method

The material for the present studies was obtained from the sources listed in Table I. Wherever possible, the identity of the material was checked with the known description of the species. Both the fresh and dried materials were used for comparison of the structure but, for preparing the illustrations, the fresh material was used. The general method of study was essentially the same as has been reported earlier (4). However, in making outline drawings with the help of Delineascope, the drawing sheet was placed on the surface of the glass screen facing the Delineascope, rather than on the opposite side as described previously. Though a bit inconvenient, this minor change avoided the reversion of the image on tracing.

Macroscopic Characteristics of the Leaves

The leaves of *L. lanata* can be distinguished from the leaves of *L. officinalis* and *L. latifolia* due to the presence of a dense indumentum of numerous, white, very large, branching hairs, and because of the slightly revolute margins. The leaves of *L. officinalis* and *L. latifolia* are very much alike except that, in *L. officinalis*, the leaves are narrower than those of typical *L. latifolia*.

The outlines of the leaves without the indumentum, are shown in Figures 1, 2, and 3 (Plate I). The leaves of *L. officinalis* and *L. latifolia* are usually dimorphic and show considerable differences in their size. The primary leaves on the young shoots in either species are up to 6 cm. or more in length. The leaves from cultivated plants were found to be considerably larger than those obtained from the wild plants. Leaves from the cultivated plants designated as *L. spica* [Fig. 4 (Plate I)] varied so much in their size that it was not possible to assign them to either *L. officinalis* or *L. latifolia*, by virtue of their size alone.

Microscopic Characteristics of the Leaves

A. *Marginal and the Apical Venation:* The leaves in all the three species show at the base a prominent midrib which is flanked on either side by two very narrow lateral veins. These lateral veins, though separated from the midrib at the base, later on join the marginal branches of the large primary veins originating from the midrib and thereafter continue to follow a marginal course towards the apices

TABLE I

LIST OF THE SOURCES OF THE MATERIAL USED IN THE STUDY

Serial No.	*Name or the synonym of the species*	*Specimen*	*Source* *	*Collector*	*Place*	*Date*
1.	L. officinalis Chaix	Fresh	L.	Authors	Lima, Pa., U.S.A.	July, 1958
2.	" (Syn. L. vera DC.)	Dried	I	Joaquim Castro	Porto, Portugal	July 30, 1948
3.	" (Syn. L. vera DC.)	Fresh	D	Curator	Royal Botanic Gardens, Kew	Sept. 29, 1959
4.	" (Syn. L. vera DC.)	Dried	A	Martindale	Byberry, Pa.	June, 1865
5.	" (Syn. L. vera DC.)	Dried	E	Endress	Villefranche, France	Sept., 1929
6.	" (Syn. L. vera DC.)	Dried	J	Through Dr. Dunn	Chicago	Aug., 1959
7.	" (Syn. L. vera DC.)	Dried	E	Bourgeau	Valle de la Segre	July, 1847
8.	" (Syn. L. vera DC.)	Dried	B	—	Pyrenees	—
9.	" (Syn. L. vera DC., L. pyrenaica DC.)	Dried	E	—	—	—
10.	L. officinalis Chaix	Dried	D	J. Sonster	Gorges de Ila	June 15, 1952
11.	L. latifolia Vill.	Fresh	D	Curator	Kew	Sept. 29, 1959
12.	L. latifolia Vill.	Fresh	K	Neugebaur	Pasadena, California, U.S.A.	July, 1959
13.	L. latifolia Vill.	Dried	E	Maihlo	Ariege	Sept. 21, 1889
14.	L. latifolia Vill.	Dried	G	Groves	Florence	1875
15.	L. latifolia Vill.	Dried	F	Reverchon	Valencia (Spain)	Aug., 1897
16.	L. latifolia Vill.	Dried	D	—	Vauciuse	Sept., 1876
17.	L. latifolia Vill.	Dried	C	—	From Spain	—
18.	" (Syn. L. spica DC.)	Dried	B	—	—	—
19.	" (Syn. L. spica DC.)	Dried	E	Bourgeau	Riopar (Spain)	July 30, 1850
20.	" (Syn. L. spica DC.)	Dried	E	Endress	Villefranche	Sept. 4, 1830
21.	" (Syn. L. spica DC.)	Dried	F	Bordere	Lourdes (Hautes, Pyrenees)	June, 1879

22.	L. lanata Boiss.	Fresh	D	Curator	Kew	Sept. 29, 1959
23.	L. lanata Boiss.	Fresh	K	Neugebaur	Pasadena, California, U.S.A.	July, 1959
24.	L. lanata Boiss.	Dried	D	Ex-Munby	Sierra Nevada (Spain)	Aug., 1848
25.	L. lanata Boiss.	Dried	D	E. Bourgeau	Sierra Nevada	July 14, 1851
26.	L. lanata Boiss.	Dried	F	E. Reverchon	Sierra de la Nieva (Spain)	Aug. 10, 1889
27.	L. lanata Boiss.	Dried	G	Porta & Rigo	—	1891
28.	L. lanata Boiss.	Dried	E	E. Bourgeau	Sierra Nevada	July 14, 1851
29.	L. lanata (?)	Dried	H	—	—	—

* A—Herbarium, Philadelphia College of Pharmacy and Science, Philadelphia.

B—Herbarium, Academy of Natural Sciences, Philadelphia.

C—Herbarium, Washington U. S. National Museum, Department of Botany, Smithsonian Institution, Washington, D. C.

D—Herbarium and the Gardens, The Royal Botanic Gardens, Kew, Richmond, Surrey, England.

E—Herbarium, Museum National d' Histoire Naturelle, Laboratoire de Phanerogamie, Paris, France.

F—Staatherbarium, München, Germany.

G—Botanischer Garten der Friedrich-Schiller, Universitat, Jena, E. Germany.

H—Orto Botanico, Universita di Napoli, Naples, Italy.

I—Instituto de Botanico, "Dr. Goncalo Sampio," Universidad de Porto, Porto, Portugal.

J—Drug Plant Garden, University of Illinois, School of Pharmacy, Chicago.

K—Private Garden of Miss Edna K. Neugebaur, Pasadena, California.

L—Garden, Tyler Arboretum, Lima, Pennsylvania.

PLATE III

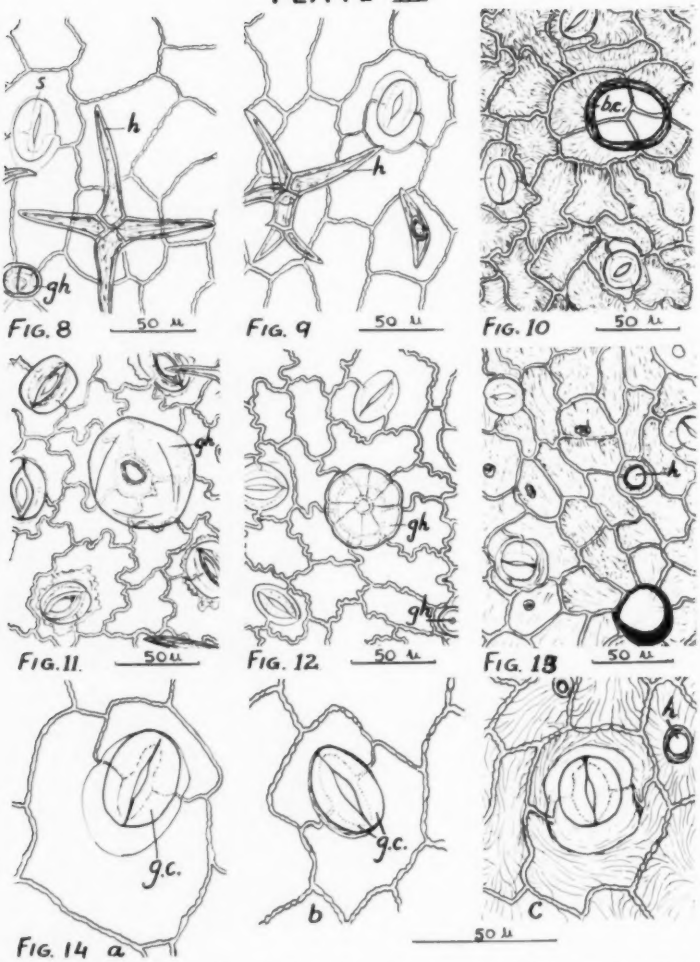


FIG. 8 FIG. 9 FIG. 10

FIG. 11. FIG. 12. FIG. 13

FIG. 14 a

Figs. 8-10. The upper epidermis in surface view: 8. *L. officinalis,* 9. *L. latifolia,* and 10. *L. lanata.*

Figs. 11-13. The lower epidermis in surface view: 11. *L. officinalis,* 12. *L. latifolia,* and 13. *L. lanata.*

Fig. 14. The stomata: (a) *L. officinalis,* (b) *L. latifolia,* (c) *L. lanata.*

(b.c., basal cell; g.c., guard cell; gh, glandular hair; h, nonglandular hair; s, stomata.)

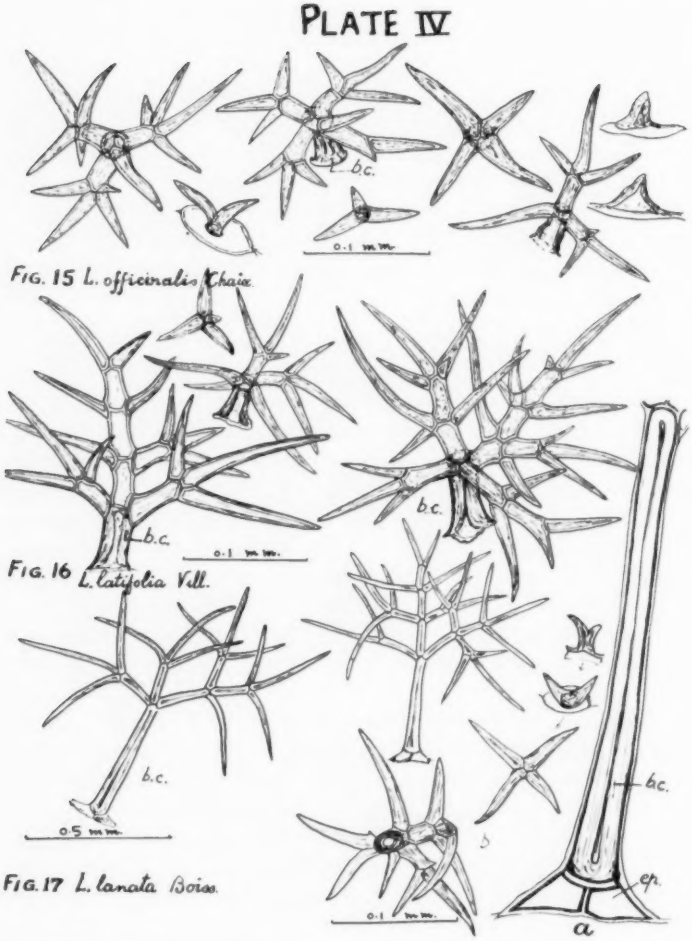
of the leaves. A closer inspection of the venation at the apices of the leaves of these species [Fig. 5 a, Fig. 6 a, and Fig. 7 a (Plate II)] shows that: (1) The type of venation in case of *L. officinalis* and *L. latifolia* are quite similar, (2) Both of these species have a brush-like tuft of vascular tissues at the terminal end of the midrib, (3) In *L. lanata,* the larger primary branches (Fig. 7 a, p.br.) near the apex originate almost opposite each other from the midrib which they later rejoin near the apex, (4) The marginal strands of vascular tissues in case of *L. lanata* form a continuous network over the apical end of the midrib [Fig. 7 a (Plate II)], and (5) The marginal venation in all the three species is almost similar [Fig. 5 b, Fig. 6 b, and Fig. 7 b (Plate II)].

B. *Surface Characteristics of the Upper and the Lower Epidermis:* The upper and the lower epidermis from the laminal regions of the leaves of the three species are shown in surface view in Figs. 8, 9, 10, and Figs. 11, 12, 13 respectively. The cells of the upper epidermis in *L. officinalis* and *L. latifolia* resemble each other very closely in their size, and in the beaded appearance of their walls [Figs. 8 and 9 (Plate III)]. The cuticle is usually smooth except at the base of some of the larger nonglandular hairs where minute striations may be seen. In *L. lanata,* however, the epidermal cells are comparatively smaller in size and show distinctly striated cuticle [Fig. 10 (Plate III)]. These two characteristics are diagnostic. The cell walls of the epidermis in *L. lanata* are beaded like the other two species.

The lower epidermis of *L. officinalis* and *L. latifolia* are also similar to each other in appearance but differ from the upper epidermis in having cells with very wavy outlines [Figs. 11 and 12 (Plate III)].

In *L. lanata,* the cells of the lower epidermis are similar to the upper epidermis but in comparison with the other species are somewhat smaller in size with more regular outlines [Fig. 13 (Plate III)]. The cuticle on the lower surface is also striated but not to the same extent as seen on the upper surface.

C. *Stomata:* The stomata in all the three species are of caryophyllaceous type and are raised above the surface of the epidermis. This is true of the stomata on either surface in each of the three species. The stomata are more numerous on the lower surface in all the three species. Sometimes the cuticle on the sides of the raised



Figs. 15-17. The nonglandular hairs: 15. *L. officinalis*, 16. *L. latifolia*, 17. *L. lanata*.

(b.c., basal cell; ep., epidermis.)

stomata shows excessive wrinkles which make the areas surrounding the stomata appear uneven and distorted.

The stomata in *L. officinalis* and *L. latifolia* have a tendency to be elliptic in shape (Fig. 14, a and b) whereas stomata in *L. lanata* are as broad as they are long, and appear to be almost circular in outline (Fig. 14 c). The pores of the stomata in case of *L. lanata* are small and very slightly elliptical to almost circular, as compared to the large elliptical to narrow slit-like pores in the other two species.

D. *Nonglandular Hairs:* The nonglandular hairs in *L. officinalis* [Fig. 15 (Plate IV)] and *L. latifolia* [Fig. 16 (Plate IV)] are similar except that the basal cells of these hairs examined in case of *L. latifolia* are larger and thicker than those of *L. officinalis.* In *L. latifolia,* the primary branches arise 2 to 3 at each node of the main axis of the hairs which usually has 3 to 4 nodes. The primary branches further give off one to two pairs of secondary branches. In *L. officinalis,* the hairs have one or sometimes two nodes on the main axis, each of the nodes having one or two pairs of primary branches. The cuticle over the constituting cells of these hairs in either species shows very minute striations or dot like projections.

In *L. lanata,* the nonglandular hairs are many times larger than the nonglandular hairs of the other two species and constitute a very important diagnostic characteristic. The basal cells of these hairs are the largest and the stoutest of all the other constituting cells [Fig. 17 a (Plate IV)]. The cell walls are very much thickened and the lumen of the cell is almost obliterated. In only one specimen, smaller branching hairs resembling similar hairs of the other species were seen [Fig. 17 b (Plate IV)]. This particular specimen, however, although labelled as *L. lanata,* did not give any information about the place or the time of collection or the name of the collector.

The basal cells of the larger nonglandular hairs in *L. lanata* are situated over two to many epidermal cells which are slightly raised above the level of the other epidermal cells [Fig. 18 a, b, c (Plate V)]. A similar condition exists underneath the larger nonglandular hairs in both *L. officinalis* and *L. latifolia.*

E. *Glandular Hairs:* Two types of glandular hairs are found in each of the three species. The smaller glandular hairs consist of single-celled stalks with two-celled globular heads, and are almost identical in the three species, except for minor variations in the size

PLATE V

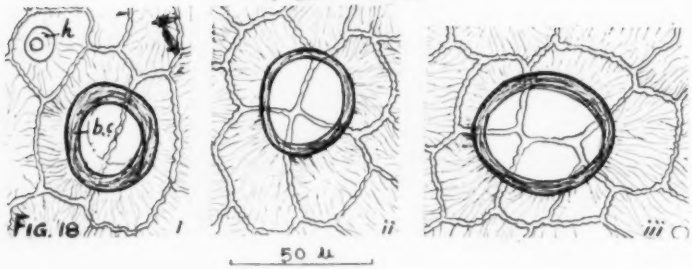


FIG. 18

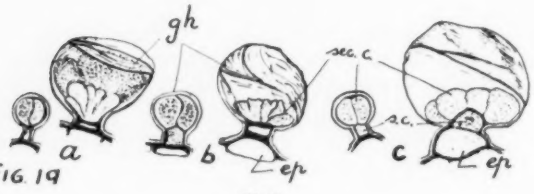


FIG 19

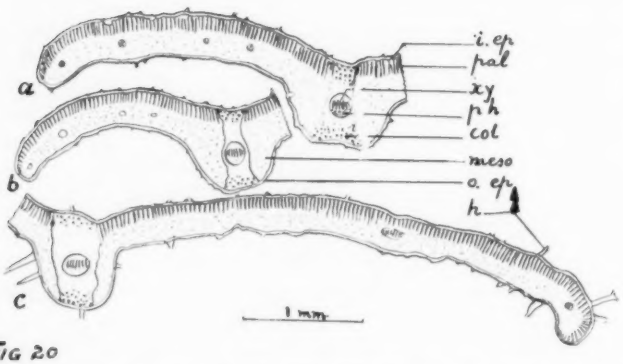


FIG 20

Fig. 18. The basal cell (b.c.) of the large nonglandular hair showing two (i), four (ii), and more than four (iii) epidermal cells underneath.

Fig. 19. The small and the large glandular hairs: (a) *L. officinalis*, (b) *L. latifolia*, and (c) *L. lanata*.

Fig. 20. Outlines of a portion of the transverse sections of the leaves: (a) *L. officinalis*, (b) *L. latifolia*, and (c) *L. lanata*.

(b.c., basal cell; col, collenchyma; ep, epidermis; gh, glandular hair; i.ep, inner or the upper epidermis; meso, spongy parenchyma; o.ep, outer or the lower epidermis; pal, palisade cells; ph, phloem; s.c., stalk cell; sec. c., secreting cells; xy, xylem.)

of the stalk cells and the diameter of the globular heads [Fig. 19 a, b, c (Plate V)].

The larger glandular hairs are usually more abundant on the lower surface and are similar in their over-all structures. These hairs consist of a small stalk cell below a group of 6 to 8 secreting cells which are enclosed within a large cutinised globular head. The stalk cell is distinctly visible only in case of *L. lanata* where it is seen to lie at the top of a dome-shaped epidermal cell (Fig. 19 c, ep) which is somewhat raised above the surface of the epidermis. In the other two species, the stalk cells are almost obliterated or, at least, not distinctly visible. In *L. officinalis,* the epidermal cell bearing the stalk cell is often slightly below the level of the epidermal surface. As compared with the other two species, the globular heads of the large glandular hairs of *L. lanata* have the greatest diameters.

Other epidermal cells surrounding the epidermal cell bearing the stalk cell of the glandular hairs are arranged in a radiating fashion and show the usual characteristics of the epidermal cells of the species.

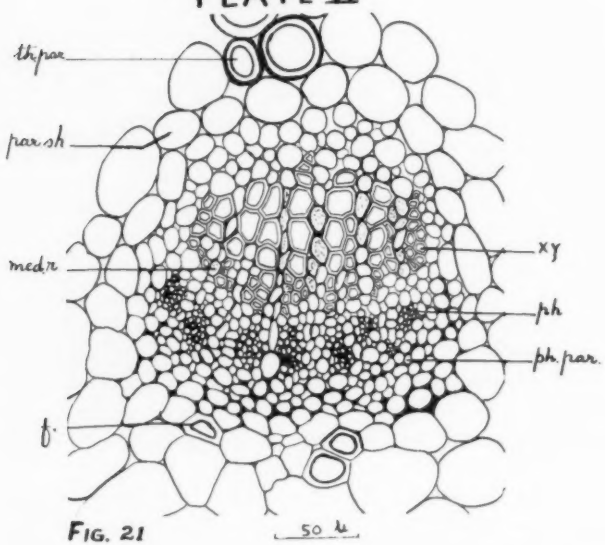
F. *Transverse Sections Through the Midrib:* The leaves of these species show a typical dorsiventral arrangement of the various tissues. The margins of the leaves are straight, slightly bent downwards, or even curved inwards on the lower surface. The midrib in all the three species is prominent and bulges downwards [Fig. 20 a, b, c (Plate V)].

In all the three species, the continuity of the 1 to 2 cell-thick palisade layer is broken in the region of the midrib due to the presence of a roughly funnel shaped zone of collenchyma which is three to five or even more cells wide at its upper end.

The upper epidermis in the region of the midrib, in all the three species, shows prominently thickened outer tangential walls [Fig. 22 (Plate VI) and Fig. 24 (Plate VII)]. In case of *L. lanata,* the cuticle in this region shows very distinct striations [Fig. 24, s. cu (Plate VII)].

The basic arrangement of the various tissues in the central vascular strand is essentially similar in all the three species and is represented here by a transverse section through the midrib region of the leaf of *L. officinalis* [Fig. 21 (Plate VI)]. Surrounding the fibrovascular bundles is a one-celled sheath of large parenchymatous cells. This, though distinct from the neighboring tissues, does not show any

PLATE VI



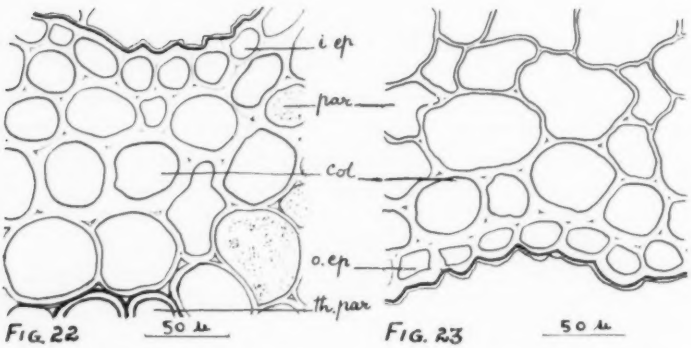


Fig. 21. Transverse section of the midrib showing the vascular tissues in *L. officinalis.*

Figs. 22-23. The upper and the lower epidermal layers, respectively, in the region of the midrib, and the adjacent collenchymatous tissues.

(col, collenchyma; f., fiberlike cell; i ep, inner epidermis; med. r., medullary ray; o.ep, outer epidermis; par, parenchyma; par. sh, parenchymatous sheath; ph, phloem; ph.par., phloem parenchyma; th.par, thick walled cells.)

characteristics, such as Casparian thickenings, of the typical endodermal cells [Fig. 21, par. sh (Plate VI)]. In *L. officinalis* alone, there are seen a few thick-walled, rounded cells on the outside of the parenchymatous sheath above the xylem and a few thick-walled cells below the phloem on the lower side.

The xylem is composed of radial rows of small fibrovascular elements separated from each other by 1- to 2-celled wide rows of pigmented and thickened cells of the medullary rays. The number of the rows of fibrovascular elements is not constant in any species and usually overlap with the number of similar rows in other species.

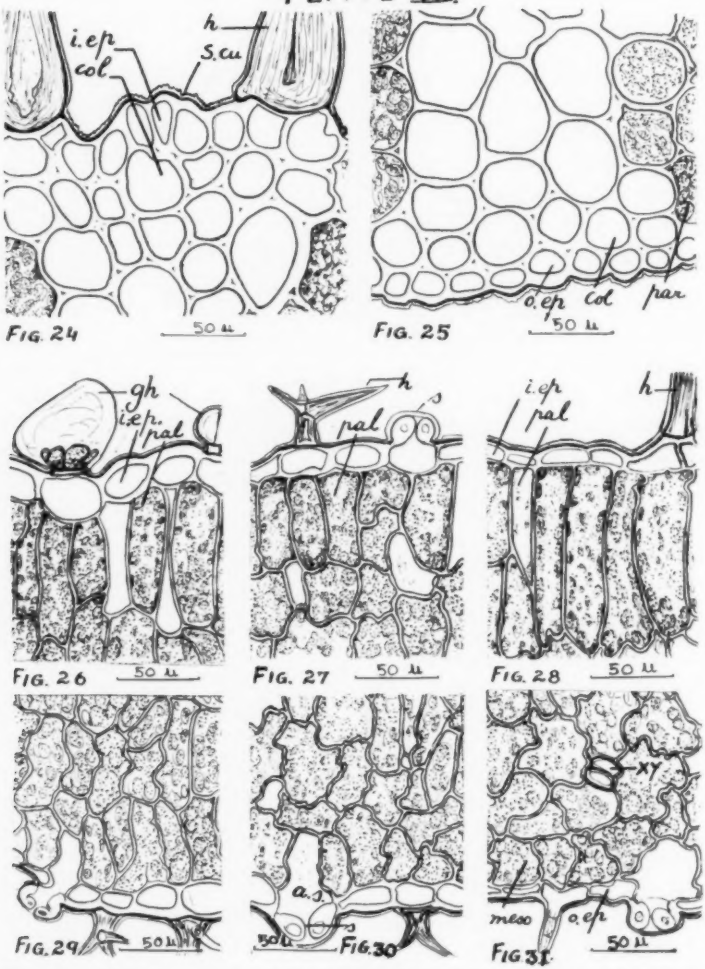
The phloem consists of small patches of sieve tube elements and compactly arranged phloem parenchyma [Fig. 21, ph & ph. par. (Plate VI)]. The medullary rays are not distinct in the phloem region.

Below the phloem tissue is a zone of thin to slightly thick-walled parenchyma which is gradually replaced by two to many rows of collenchymatous tissue [Fig. 23 (Plate VI)]. The lower epidermis in all the three species show thickened outer tangential walls [Fig. 23 (Plate VI) and Fig. 25 (Plate VII)]. In *L. lanata,* the cuticle is markedly striated compared to the other two.

G. *Transverse Section Through the Lamina:* Portions of transverse sections closer to the upper epidermis of the three species are shown in Figs. 26, 27, and 28 (Plate VII). The epidermal cells in case of *L. officinalis* (Fig. 26) are comparatively larger in size and show thicker outer tangential walls. The stomata and the hair bases are of the types already described elsewhere in this report. The palisade cells are much more elongated in case of *L. lanata* (Fig. 28) but may be one or two-layered deep in all of the three species.

The arrangement of the tissues near the lower epidermis in these species is shown in Figs. 29, 30, and 31 (Plate VII). The cells of the spongy mesophyll of *L. officinalis* (Fig. 29) are more or less elongated and somewhat palisadelike compared to the irregular outlined parenchyma of the mesophyll of the other species. The palisade cells, as also the parenchymatous mesophyll cells, are rich in chlorophyll pigment.

PLATE VII.



Figs. 24 and 25. The upper and the lower epidermal layers in the region of the midrib in *L. lanata.*

Figs. 26-28. Transverse sections of the lamina showing the upper epidermis and the palisade cells: 26. *L. officinalis,* 27. *L. latifolia,* and 28. *L. lanata.*

Figs. 29-31. Transverse sections of the lamina showing the lower epidermis and the spongy parenchyma: 29. *L. officinalis,* 30. *L. latifolia,* and 31. *L. lanata.*

(a.s., air space; col, collenchyma; gh, glandular hair; h, nonglandular hair; i.ep, inner or upper epidermis; meso, spongy parenchyma; o.ep, outer or the lower epidermis; pal, palisade cells; par, parenchyma; s, stomata; s. cu, striated cuticle; xy, xylem.)

Conclusion

Morphological characteristics of the leaves of the three members of the section, *Spica*, are not adequate to separate these species from one another. Leaves of *L. officinalis* and *L. latifolia* resemble each other very closely. In cultivated plants of these species, there is much variation in the size of the leaves. Leaves of *L. lanata* possess characteristic nonglandular hairs which are quite distinct from similar hairs found on the other two species. Also, the epidermal surfaces in case of *L. lanata* show distinctly striated cuticle. These two characteristics may be used to distinguish *L. lanata* from the leaves of *L. officinalis* and *L. latifolia*. In addition, the smaller size and more regular outlines of the epidermal cells of *L. lanata* may also be useful histologically.

Summary

In this report, the histological characteristics of the leaves of *L. officinalis Chaix, L. latifolia Vill.*, and *L. lanata Boiss.* are briefly described and illustrated. The venation in the terminal ends and the marginal sides of the leaves is compared. The surface characteristics of the upper and the lower epidermis of the laminal region, the shape and form of the glandular and the nonglandular hairs, the types of the stomata, and the basal regions of the nonglandular hairs are described and illustrated. Transverse sections through the midrib and the laminal portions are described and illustrated.

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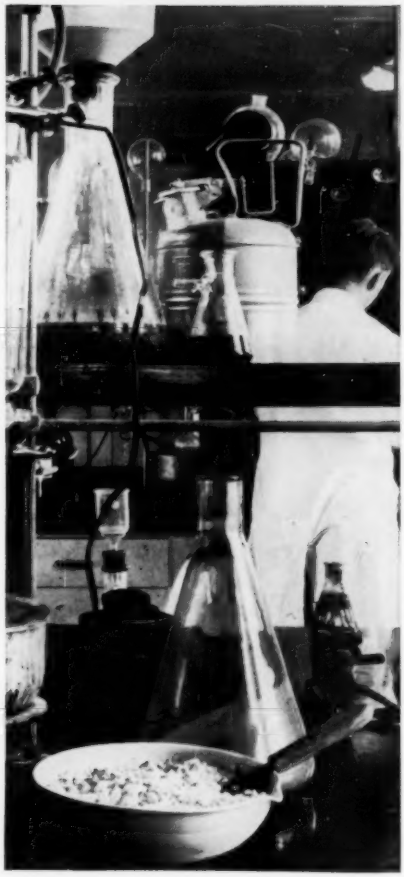

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